Original article

Incobotulinum toxin type A for treatment of chronic myofascial pain

Jorge Chaurand¹⁾, Marycarmen Godínez-Victoria²⁾, Aldo Tellez-Girón¹⁾, Jose-Alfredo Facio-Umaña³⁾, and Fiacro Jimenez-Ponce⁴⁾

¹⁾Maxillofacial Surgery Department, National Medical Center "20 de Noviembre" Institute for Social Security and Services for State Workers, México City, México

²⁾Research Department, Superior School of Medicine, National Polytechnic Institute, México City, México

³⁾Research Department, School of Dentistry, Autonomous University of Coahuila, Torreón, Coahuila, México

⁴⁾Regulatory and Attention to Hospitals Department, Institute for Social Security and Services for State Workers, México City, México

(Received March 5, 2020; Accepted May 14, 2021)

Abstract

Purpose: This study assessed the effectiveness of incobotulinum toxin type A (IBTx) for chronic myofascial pain affecting the masseter and temporal muscles.

Methods: Twenty two patients who received a diagnosis of chronic masseter and temporalis myofascial pain were evaluated by using a visual analog pain scale (VAS), digital pressure algometry, and the SF-36 Health Survey at baseline (T0), before IBTx injection. Patients were again evaluated at 2 months (T1) and 7 months (T2) after IBTx injection.

Results: VAS scores for pain significantly differed ($P = 0.029$, Friedman test). *Post-hoc* tests showed a significant reduction in pain at 2 months (T0–T1) and 7 months (T0–T2) ($P = 0.011$ and $P = 0.028$, respectively; Wilcoxon test) but not between 2 and 7 months ($P = 0.676$; Wilcoxon test). There was no significant difference in pressure algometry values ($P = 0.385$, Friedman test). Quality of life (QOL) assessment showed a significant difference ($P = 0.002$, Friedman test). *Post-hoc* tests showed a significant improvement in QOL at 2 months, but no significant difference at 7 months ($P = 0.004$ and $P = 0.260$, Wilcoxon test).

Conclusion: IBTx injection resulted in safe, effective short-term pain relief for patients with chronic facial pain affecting the masseter and temporalis muscles.

Keywords; botulinum toxin, myofascial pain, temporomandibular joint disorders

Introduction

Myofascial pain (MP) is the most common cause of persistent regional pain, such as back pain, shoulder pain, tension-type headache, and facial pain [1]. Estimates indicate that 42% of temporomandibular disorder (TMD) diagnoses are attributable to MP [2]. About 70% of patients who present to secondary care for management of TMD can be adequately and appropriately treated without surgical treatment [3]. Patient education, pharmacological therapy, psychotherapy, noninvasive interventions (including physiotherapy), and application of a splint have been advocated. Nevertheless, some patients show no improvement with conservative treatment and usually seek other treatments for pain relief. When pain becomes refractory or chronic (duration greater than 6 months), diagnosis and treatment are more complicated. Chronic pain is not a symptom: it is a disease [4,5] that is often worsened by the unpredictability of treatment. Misunderstanding the meaning of symptoms, and negative expectations of recovery, may lead to anxiety and depression, thereby worsening the pain response [6]. The clinical characteristics of MP include hard, palpable, discrete, localized nodules—called trigger points (TrPs)—which are painful and

can be active or latent, and localized or with referral. Increased local-tissue density in the form of contraction knots may result from increased muscle fiber contraction and recruitment and local injury [1].

Botulinum toxin injections can improve blood flow to muscle and release nerve fibers compressed by abnormally contracting muscle, both of which contribute to pain [7]. Botulinum toxin injections can have an immediate effect because introduction of the needle causes endogenous endorphins to be released directly, and because the balance of central neurotransmitters is altered. This is caused by local inhibition of pain peptides from sensory ganglions and nerve terminals, and anti-inflammatory and anti-glutamatergic action [8]. A systematic review and meta-analysis found moderate evidence for the efficacy of botulinum toxin in treating trigeminal and postherpetic neuralgia [9], suggesting another mechanism for pain relief. Independent of its neuromuscular effects, botulinum toxin may inhibit release of local nociceptive neuropeptides, neurogenic inflammation, and peripheral sensitization [10].

Use of botulinum toxin injections for MP treatment has been widely reported [11]. The results have been contradictory, and although some evidence suggests a benefit [2,9], some clinicians choose not to use botulinum toxin because of the cost, limited duration of effect, lack of evidence, and adverse reactions, among other reasons [12].

This study analyzed a sample of 22 patients with chronic MP. IBTx was evaluated over a period of 7 months, to analyze its effect during the "active", 4- to 6-month period. The evaluation period was extended to 7 months to evaluate the effects of IBTx after its duration of action. An IBTx formulation without an added protein complex and with different storage and transportation requirements was used in order to reduce cost and adverse reactions.

Materials and Methods

This clinical trial was conducted during the period from October 2017 through October 2018. The sample size was calculated by using data (mean difference) from the author's previous work [13]. The study included 22 adults selected by consecutive sampling (every participant meeting the inclusion criteria was recruited until the required sample size was achieved). Patients were included if they had received a diagnosis of chronic bilateral MP and had at least 4 TrPs per side (minimum of 6 months with no response to conservative treatment), in accordance with the Diagnostic Criteria for the Most Common Pain-Related Temporomandibular Disorders (DC/TMD; ICD-9729.1). Patients with joint conditions, according to the DC/TMD, such as joint pain, joint disorders (e.g. disc disorders, hypomobility disorders, hypermobility disorders, subluxation), joint diseases (degenerative joint disease, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, idiopathic condylar resorption, osteochondritis dissecans, osteonecrosis, neoplasm, synovial chondromatosis), fractures, congenital or developmental disorders, and systemic inflammatory connective tissue diseases (eg, myasthenia gravis, Lambert–Eaton syndrome, lateral sclerosis amyotrophic), and patients with a previous history of botulinum toxin injections, were excluded. All patients underwent a 3-stage assessment for the clinical trial before 1 month of no pharmaceutical treatment (only physiotherapy and/or splint were allowed, and then withdrawn). A baseline evaluation (T0) was conducted immediately after IBTx injection, and follow-up evaluations were performed at 2 months

Correspondence to Dr. Jorge Chaurand, Maxillofacial Surgery Department, National Medical Center "20 de Noviembre" Institute for Social Security and Services for State Workers, Av. Félix Cuevas 540 Colonia del Valle, México City 03100, México
E-mail: jorge.chaurand@issste.gob.mx

J-STAGE Advance Publication: December 9, 2020

Color figures can be viewed in the online issue at J-STAGE.

doi.org/10.2334/josnusd.20-0090

DN/JST.JSTAGE/josnusd/20-0090

Fig. 1 Boxplot of VAS pain evaluation at 3 time points ($P = 0.029$, Friedman test)

(T1) and 7 months (T2).

Measurements were made by one of the authors (A.T.G.), and IBTx was injected by J.CH., both of whom were unblinded to the disease status of the patients. This study was conducted in accordance with the Declaration of Helsinki and was approved by the regional Ethical Review Board of the National Medical Center “20 de Noviembre” Institute for Social Security and Services for State Workers (ISSSTE) approved the study (approval no. 441.2017), and all participants gave their written informed consent.

Baseline data recordings

Each patient answered the SF-36 Health Survey and underwent a clinical examination comprising palpation of the temporal and masseter muscles. Only these 2 muscles were included in the search for TrPs because of the reproducibility of the findings, joint pain on movement, and the presence of joints sounds could be used to rule out other sources of pain. Two TrPs in the masseter and 2 TrPs in the temporalis muscles per side were localized by physical examination and recorded on a printed map (total, 8 TrPs per patient).

A visual analogue scale (VAS) was used to assess pain: 0 indicates no pain and 10 the worst pain ever. VAS scores were recorded as the primary outcome, and digital pressure algometry readings for each TrP were used as the secondary outcome. A digital pressure algometer (Imada, IL, USA) was used to assess muscle tenderness of selected components in the masticatory motor system, such as the superficial and deep masseter muscle, and anterior or posterior temporal muscle. Examination of these muscles was performed extraorally. Algometric measurements were performed by A.T.G. During the examination, the footplate of the algometer was held perpendicular to the skin, at the trigger point of the examined muscle, and a constant force was applied until the patient reported pain (pressure pain threshold). The resultant reading (in kilograms) was recorded for each TrP, after which IBTx was injected.

Botulinum toxin injections

The drugs and syringes were prepared by a research assistant, and the solution was prepared by dissolving 100 IU IBTx (Xeomeen) into 1 mL of sterile saline solution (0.9%) at room temperature. This was done immediately before injection. A 1-mL insulin syringe with a hypodermic needle was used for the injections. In a single session, each patient (4 TrPs on each side; left and right) was injected with 100 IU of IBTx by J.CH., as follows: 15 IU for each TrP in the masseter and 10 IU for each TrP in temporalis muscle. Patients were instructed not to perform massage or apply hot or cold packs to the area. The present authors conducted a previous study [13] in which a total IBTx dose of 100 IU was used. A positive effect was obtained after 1 month; thus, the present study evaluated the effect of the same dose at 7 months.

Data recordings

After the baseline evaluation (T0) and IBTx injection, all patients were prescribed celecoxib 100 mg for pain. No muscle relaxants, tricyclic antidepressants, or other drugs were given to any patient. Previous physiotherapy or splints were withdrawn.

After 2 months (T1) and 7 months (T2), pressure algometry (at the

Fig. 2 Boxplot of QOL evaluation at 3 time points ($P = 0.002$, Friedman test)

bilateral muscle sites identified by mapping and confirmatory clinical exploration), VAS, and the SF-36 Health Survey were repeated. The sum of the TrP recordings was used in the statistical analysis. In the final evaluation, patients were asked if they wanted a new IBTx injection, which was administered in the event of an affirmative response.

Statistical analysis

The data were not normally distributed when evaluated with the Shapiro–Wilk test and were therefore analyzed with the Friedman test. The Wilcoxon test was used for *post-hoc* analysis of VAS, pressure algometry, and quality of life (QOL) (SF-36). A P value of less than 0.05 was considered to indicate statistical significance. The measurements were reported in boxplot dispersion diagrams.

Results

Twenty-four patients were initially included in the study; 1 patient was excluded from the analysis because of admission to hospital for other reasons. Another patient was excluded for taking a nonapproved medication. Thus, data from 22 patients were ultimately included in the analysis; 19 (86%) were female and 3 (14%) were male. Mean age was 54.39 ± 11.04 years. The average duration of symptoms was 31.78 ± 19.83 months. One patient reported severe pain at the time of injection.

VAS scores for pain significantly differed ($P = 0.029$, Friedman test; Fig. 1). *Post-hoc* tests showed a significant reduction in pain at 2 months (T0–T1) and 7 months (T0–T2) ($P = 0.011$ and $P = 0.028$, respectively; Wilcoxon test) but not between 2 and 7 months ($P = 0.676$, Wilcoxon test). There was no significant difference in pressure algometry values ($P = 0.385$, Friedman test).

QOL assessment

The SF-36 Health Survey includes items related to limitations of activities, physical health problems, emotional health problems, social activities, pain, energy and emotions, and general health; 0 is the worst score and 100 is the best score (ie, better QOL). The sum of all items for each patient was used in the statistical analysis. There was a significant difference ($P = 0.002$, Friedman test; Fig. 2). *Post-hoc* testing showed a significant improvement in QOL only at 2 months, and no significant difference at 7 months ($P = 0.004$ and $P = 0.260$, respectively; Wilcoxon test). Spearman correlation analysis showed no significant difference ($r_s = -0.120$, $P = 0.338$) between pain VAS score and QOL.

At the 7-month evaluation, VAS and QOL values tended to return to baseline values: 7.60 ± 1.47 (T0) and 7.13 ± 1.47 (T2) for VAS, and 47.58 ± 16.52 (T0) and 52.25 ± 15.21 (T2) for QOL. At the 7-month evaluation, patients were asked if they wanted a new IBTx injection; 6 patients (27%) responded that “they feel better with it”, and 16 patients (73%) declined a second injection because they “did not feel pain as before”.

Discussion

IBTx type A is a neurotoxin that lacks the added protein complex included in other brands and preparations. This reduces immunogenic potential

Fig. 3 Proposed pathophysiological model of disease. The sequence differs in relation to patient characteristics.

and results in different transportation and storage requirements. A cost-effectiveness study [14] reported good outcomes in comparison with those of onabotulinum toxin type A. Only one study [13] using IBTx for MP in temporal and masseter muscles reported good short-term outcomes. Although the cost is higher than that of conservative treatment (e.g. splints), the effectiveness of oral appliances for chronic TMD has not been proven, and potential side effects have been reported, including increased muscle activity, increased load on the temporomandibular joint (TMJ), open bite, and supereruption of teeth [15]. Furthermore, variability in appliance design and patient cooperation may contribute to inconsistent success rates. A cost-benefit study focusing on facial pain is necessary in order to clarify this issue.

When analyzing duration of treatment, a systematic review and meta-analysis that included only placebo (normal saline solution)-controlled studies [16] reported that botulinum toxin injections reduced pain at 2 to 6 months, but not at 4 to 6 weeks. The primary outcome was pain, as evaluated by VAS; pressure algometry was the secondary outcome. In this systematic review, no study used IBTx type A, and no study had a follow-up period longer than 6 months. The results for the primary outcome measure were consistent with those of the present study: at 2 months, pain had decreased and QOL was better. These positive effects appeared to diminish at 7 months. However, in contrast with the systematic review [16], which included neck muscles, the present results showed no significant difference in masticatory muscle pressure algometry values between groups. This indicates that other methods of evaluation should be encouraged (e.g. brain cortex imaging, blood markers, needle electromyography, MRI apparent diffusion coefficient). Another recent systematic review [2], which included various injected drugs and dry puncture for TMD pain, identified 8 studies of botulinum toxin: 3 found that botulinum toxin was ineffective for the assessed outcome, and 5 reported limited benefit. No study used IBTx or had a follow-up period much longer than 6 months. Any treatment is subject to the placebo effect, and the absence of a control group in this study makes it impossible to exclude the possibility of such an effect. A control group with saline injection or dry needling was not possible, for ethical reasons. However, the results obtained in this study suggest that once the vicious cycle of pain was broken, the duration of action of IBTx could be greater than 6 months, apparent with 73% of the sample. In addition, patient bias resulting from expectations of a treatment effect and the fluctuating course of TMD are concerns. A placebo-controlled study (blinded for patients and examiners) with a longer follow-up period might yield more-accurate data.

Although the effect was positive for the present patients, with or without a new injection of IBTx, at the end of the study, does this justify the use of IBTx for treatment of chronic MP? The requirements of evidence-based medicine and statistical analysis would suggest not, but the clinical setting is more complex and real-world patients differ from those enrolled in randomized clinical trials, as explained by Sandrini [17]. Repeat injections might not always be necessary, as indicated in the present study. In addition,

use of the present formulation reduces adverse reactions and potential harms. No severe adverse reactions were reported by any of the present patients. Use of celecoxib for pain during the study and classification or assignment of patients with chronic pain as having a single (muscle-related) condition are potentially confusing because combined joint and muscle pain could be present even if clinical findings indicate that pain is primarily muscle-based [18].

Another important factor that affects treatment outcomes in most TMD patients is limited understanding of MP and TMD pathogenesis. Why do muscles start to contract repeatedly and produce painful symptoms? The TMJ is continuously loaded, even when not functioning, and needs to be biomechanically sound to withstand the high mechanical loading to which it is subject [19]. Therefore, muscle contraction and joint loads are needed in order to produce the pumping action, diffusion, and nutrition of chondrocytes, which maintain the balance between TMJ structures.

Many specialists agree that chronic joint overload can produce TMJ symptoms [20], but what about underloading? Human jaws begin to work immediately after birth (breastfeeding), and as growth continues diet becomes solid and fibrous. The TMJ and muscles normally develop in an equilibrated manner [21]. However, recent animal studies [22] suggest that a soft diet and processed foods, which are common in young populations, impede mandibular and TMJ growth. The biology of the condyle is significantly modified in response to environmental changes, and the articular fossa may alter its shape and position in response to these environmental changes and undergo compensatory remodeling [23]. Therefore, temporomandibular joints might not receive “sufficient” loading and proper biomechanical actions to grow (as needed for children) and maintain physiological balance during adulthood. Muscular contractions are an alarm or protective mechanism [15,20] and may occur as an attempt to activate the hydraulic system inside the TMJ or develop a better condyle-fossa physiological relationship. A recent study used polysomnography and electromyography to evaluate muscular masticatory activity during sleep in adults [18]. The authors found elevated activity in myalgia patients and the control group. Parafunctions are thus present during the day, and also at night, when the patient is unaware, probably as a protective mechanism. In contrast, lower muscle activity may be a result of attempts to avoid joint pain (pain adaptation model) [24], as observed in patients with chronic pain who avoid eating hard foods. This could lead to TMJ underload. Many patients maintain balance or have the capacity to heal; among those who do not, symptoms can appear. Several other factors are related to masticatory muscular hyperactivity—isolated or combined—including stress [25,26], premature tooth loss, severe malocclusion [27], systemic disease, bruxism [28], medication intake, mouth breathing, and sleep disorders [29], and must be taken into account. Although it is unlikely that all patients with TMD have TMJ underload, a genetic predisposition could be present [30]. In addition, overload and underload may coexist in both joints in the same patient (left and right sides) or within each TMJ (underload during the day and overload at night). These biomechanical changes in the TMJ can cause muscle imbalance, pain, peripheral and central sensitization, cartilage degradation, and, ultimately, osteoarthritis [31]; however, the sequence differs in relation to patient characteristics. To encourage further research, a pathophysiological model of disease is proposed (Fig. 3).

Some studies [32] of patients with chronic pain suggest that addressing joint and muscle disease simultaneously is promising. However, these results need to be replicated in future studies. Muscle physiotherapy and consumption of a “normal” diet to break pain avoidance behavior is recommended, once symptoms have decreased after an intervention (IBTx injection and/or arthroscopy). This ensures physiological or necessary joint loading of the TMJ.

In conclusion, IBTx injection appears effective for treatment of chronic facial pain affecting the masseter and temporalis muscles. Some patients will need additional injections after 6 months; others will not and can return to conservative treatment. In addition, IBTx injection can be used in conjunction with other therapies (e.g. orthodontics, arthroscopy, orthognathic surgery). Future studies should attempt to clarify the pathogenesis and means of prevention of muscular pain. The mechanism by which IBTx reduces pain is not well understood, so clinical decisions need to be made carefully. Nevertheless, it seems that the present formulation does not produce severe adverse effects.

Conflict of interest

None declared.

References

- Friction J (2016) Myofascial pain mechanisms to management. *Oral Maxillofac Surg Clin North Am* 28, 289-311.
- Machado E, Machado P, Wandscher VF, Marchionatti AME, Zanatta FB, Kaizer OB (2018) A systematic review of different substance injection and dry needling for treatment of temporomandibular myofascial pain. *Int J Oral Maxillofac Surg* 47, 1420-1432.
- Rajapakse S, Ahmed N, Sidebottom AJ (2017) Current thinking about the management of dysfunction of the temporomandibular joint: a review. *Br J Oral Maxillofac Surg* 55, 351-356.
- Nugraha B, Gutenbrunner C, Barke A, Karst M, Schiller J, Schäfer P et al. (2019) The IASP classification of chronic pain for ICD-11 functioning properties of chronic pain. *Pain* 160, 88-94.
- Benoliel R, Svensson P, Evers S, Wang S-J, Barke A, Korwisi B et al. (2019) The IASP classification of chronic pain for ICD-11 chronic secondary headache or orofacial pain. *Pain* 160, 60-68.
- Heir GM (2018) The efficacy of pharmacologic treatment of temporomandibular disorders. *Oral Maxillofac Surg Clin North Am* 30, 279-285.
- Jabbari B (2008) Botulinum neurotoxins in the treatment of refractory pain. *Nat Clin Pract Neurol* 4, 676-685.
- Aoki KR (2003) Evidence for antinociceptive activity of botulinum toxin type A in pain management. *Headache* 43, Suppl. 1, S9-S15.
- Shackleton T, Ram S, Black M, Ryder J, Clark GT, Enciso R (2016) The efficacy of botulinum toxin for the treatment of trigeminal and postherpetic neuralgia: a systematic review with meta-analyses. *Oral Surg Oral Med Oral Pathol Oral Radiol* 122, 61-71.
- Aoki KR (2005) Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. *Neurotoxicology* 26, 785-793.
- Chen YW, Chiu YW, Chen CY, Chuang SK (2015) Botulinum toxin therapy for temporomandibular joint disorders: a systematic review of randomized controlled trials. *Int J Oral Maxillofac Surg* 44, 1018-1026.
- Laskin DM (2018) The use of botulinum toxin for the treatment of myofascial pain in the masticatory muscles. *Oral Maxillofac Surg Clin North Am* 30, 287-289.
- Chaurand J, Pacheco-Ruiz L, Orozco-Saldivar H, López-Valdés J (2017) Efficacy of botulinum toxin therapy in treatment of myofascial pain. *J Oral Sci* 59, 351-356.
- Tilden D, Guarnieri C (2016) Cost-effectiveness of incobotulinumtoxin-A with flexible treatment intervals compared to onabotulinumtoxin-A in the management of blepharospasm and cervical dystonia. *Value Health* 19, 145-152.
- Greene CHS, Menchel HF (2018) The use of oral appliances in the management of temporomandibular disorders. *Oral Maxillofac Surg Clin North Am* 30, 265-277.
- Khalifeh M, Mehta K, Varguise N, Suarez-Durall P, Enciso R (2016) Botulinum toxin type A for the treatment of head and neck chronic myofascial pain syndrome: a systematic review and meta-analysis. *J Am Dent Assoc* 147, 959-973.
- Sandrini G, De Icco R, Tasorelli C, Smania N, Tamburin S (2017) Botulinum neurotoxin type A for the treatment of pain: not just in migraine and trigeminal neuralgia. *J Headache Pain* 18, 38.
- Santiago V, Raphael K (2019) Absence of joint pain identifies high levels of sleep masticatory muscle activity in myofascial temporomandibular disorder. *J Oral Rehabil* 46, 1161-1169.
- Tamimi D, Kocasarac HD, Mardini S (2019) Imaging of the temporomandibular joint. *Semin Roentgenol* 54, 282-301.
- Israel HA (2016) Internal derangement of the temporomandibular joint: new perspectives on an old problem. *Oral Maxillofac Surg Clin North Am* 28, 313-333.
- Sciote JJ, Horton MJ, Rowleson AM, Ferri J, Close JM, Raoul G (2012) Human masseter muscle fiber type properties, skeletal malocclusions, and muscle growth factor expression. *J Oral Maxillofac Surg* 70, 440-448.
- Fujita Y, Maki K (2018) Association of feeding behavior with jaw bone metabolism and tongue pressure. *Jap Dent Sci Rev* 54, 174-182.
- Owtad P, Park JH, Shen G, Potres Z, Darendelier MA (2013) The biology of TMJ growth modification: a review. *J Dent Res* 92, 315-321.
- Lund JP, Donga R, Widmer CG, Stohler CS (1991) The pain-adaptation model: a discussion of the relationship between chronic musculoskeletal pain and motor activity. *Can J Physiol Pharmacol* 69, 683-694.
- Connelly ST, Myung J, Gupta R, Tartaglia GM, Gizdulich A, Yang J et al. (2017) Clinical outcomes of Botox injections for chronic temporomandibular disorders: do we understand how Botox works on muscle, pain, and the brain?. *Int J Oral Maxillofac Surg* 46, 322-327.
- Ohrbach R, Michelotti A (2018) The role of stress in the etiology of oral parafunction and myofascial pain. *Oral Maxillofac Surg Clin North Am* 30, 369-379.
- Manfredini D, Segù M, Arveda N, Lombardo L, Siciliani G, Rossi A et al. (2016) Temporomandibular joint disorders in patients with different facial morphology. A systematic review of the literature. *J Oral Maxillofac Surg* 74, 29-46.
- Manfredini D, De Laat A, Winocur E, Ahlberg J (2016) Why not stop looking at bruxism as a black/white condition? Aetiology could be unrelated to clinical consequences. *J Oral Rehabil* 43, 799-801.
- Almoznino G, Benoliel R, Sharav Y, Haviv Y (2017) Sleep disorders and chronic craniofacial pain: characteristics and management possibilities. *Sleep Med Rev* 33, 39-50.
- Mercuri LG (2017) Temporomandibular joint disorder management in oral and maxillofacial surgery. *J Oral Maxillofac Surg* 75, 927-930.
- Israel HA, Diamond B, Saed-Nejad F, Ratcliffe A (1999) The relationship between parafunctional masticatory activity and arthroscopically diagnosed temporomandibular joint pathology. *J Oral Maxillofac Surg* 57, 1034-1039.
- Thomas NJ, Aronovich S (2017) Does adjunctive botulinum toxin A reduce pain scores when combined with temporomandibular joint arthroscopy for the treatment of concomitant temporomandibular joint arthralgia and myofascial pain? *J Oral Maxillofac Surg* 75, 2521-2528.